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Oral dissolving films: an effective tool for fast therapeutic action

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ABSTRACT

The oral route is most familiar route as it has low cost of therapy and helps in the ease of administration of therapeutic agents which lead to high levels of patient compliance. The most known oral solid dosage forms are tablets and capsules. Many patients' particularly pediatric and geriatric patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is identified to afflict nearly 35% of the general population. To reduce these difficulties, the growth of several fast dissolving drug delivery systems has been produced. Oral dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly dissolves on tongue or buccal cavity. The film overcomes the danger/fear of choking. An ideal film should have the characteristics like pleasant taste, high stability, ease of handling and administration, no water necessary for administration. The present review focuses on hydrophilic polymers, plasticizers, sweeteners, flavors and colors etc which are used in the formulation of oral dissolving films including the manufacturing aspects of oral dissolving film like solvent casting method, rolling method, extrusion method and solid dispersion method and evaluation parameters like disintegration, dissolution, tensile strength, thickness, folding endurance, elastic modulus for oral dissolving films.

Keywords: Fast dissolving film, dysphagia, pediatric, hydrophilic polymers.

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I. INTRODUCTION

In solid dosage forms, some patients have major problem in the use of tablets was swallowing or chewing which forms risk or fear of chocking. In the oral delivery of drug, oral dissolving film is a new drug delivery system. Oral film a type of film which is utilized in severe condition such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and Asthma etc. Oral dissolving film has attained popularity due to its availability in various size and shape [1]. Oral dissolving films are meant to disintegrate or dissolve within seconds. They provide advantages like administration without water, rapid onset of action and convenience of dosing. For fast dissolving dosage forms, active pharmaceutical ingredients absorption is feasible through the oral mucosa and may improve bioavailability [2].

II. The concept of oral dissolving film (ODF)

- This delivery system composed of a thin film.
- After keeping it on the top of the tongue, the film dissolves within seconds, promoting first pass metabolism as estimated to tablet and other immediate release oral solid dosage forms, and may enhance the bioavailability of drug [3].
- ODF dissolves in the mouth like a cotton candy.

III. The benefits of oral dissolving film (ODF) when compared with fast dissolving film (FDT)

- Accessibility of larger surface area that drives to faster disintegration and dissolution in the oral cavity within seconds [4].
- During transportation and storing of ODF, they don't need any kind of special protection as they are flexible when compared with fast dissolving tablets as they are fragile.
- Among dysphasic patients, negative requirement of water had led to satisfactory results for ODF.
- Usage of ODF gives no fear of chocking when compared with fast dissolving tablets.
- The considerable surface area present in the film dosage form gives rapid wetting by saliva and quickly disintegrates which dissolve and absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism and on enhancement the bioavailability [5].

- As per convenience of the individual, the dosage form can be consumed at any place and any time.
- The first pass effect can be ignored, so a decrease in the dose which can guide to reduction in side effects associated with the molecule [6].
- Patients suffering from dysphagia, repeated emesis, hypertension, heart attack, asthma, motion sickness, paralysis and mental disorders favor this dosage form as they are not capable to swallow large quantities of water.

IV. Formulation of oral dissolving films:

The oral dissolving films composition is given in table 1.

Table 1: Composition of Fast Dissolving Film [7, 8]

S.No	Ingredients	Amount(w/w)
A.	Active Pharmaceutical ingredients	5 to 30 %
B.	Water soluble polymer / Film forming polymer	45 %
C.	Plasticizer	0 to 20 %
D.	Strip forming polymers	15 %
E.	Saliva stimulating agent	2 to 6 %
F.	Surfactant	q.s
G.	Sweetening agent	3 to 6 %
H.	Flavours, colors, fillers	q.s

A. Active Pharmaceutical Ingredient

The area of drug loaded film should be between 1-20 cm^2 which depends on the amount of water-soluble polymers that are responsible for faster disintegration. The oral strip technology has the potential to deliver different variety of APIS. A number of molecules can be incorporated into this delivery system. They may contain cough/cold remedies (antitussives, expectorants), anxiety drugs, cardiovascular agents, sore throat, erectile dysfunction drugs, anti-histamines, anti-asthmatics, gastrointestinal disorders, nausea, pain, CNS (e.g. anti-parkinson's disease). Other applications contain caffeine strips, snoring aid, multivitamins, sleeping aid etc. As the size of dosage form has limitation, high dose molecules are difficult to administer in oral strip. Generally 5%w/w to 30%w/w of active pharmaceutical ingredients can be administered in oral strip.

It is always useful to have micronized API which will enhance the texture of the film and also for better dissolution and uniformity in the oral strip. In these oral strip technologies, APIs are more potential and have bitter taste. This forms the formulation unpalatable mainly for pediatric preparations. Thus, before administering the API in the oral strip, the taste should be masked. Various approaches can be used to improve the palatability of the combination. Certain pathologies need instantaneous release of the medicament for prompt relief. For instance, in the case of migraine enhanced clinical effect is desired by the individual. Regiospecific delivery of the medicament would be needed in the case of sore throat, cough, allergy and other local oral manifestations. Some of the examples of suitable drug molecule that can be administered in the oral strip are listed in following table 3.

Table 3: Examples of Suitable Drug Molecule that can be Incorporated in Oral Strip

Molecule	Therapeutic Category	Dose
Chlorpheneramine maleate	Anti-allergic	4mg
Zolmitriptan	Anti-migraine	2.5mg
Cetrizine	Anti-histaminic	5 to 10mg
Famotidine	Antacid	10mg
Loperamide	Anti-diarrhoeal	2mg
Ketoprfen	Analgesic	12.5mg
Dicyclomine	Muscle relaxant	25mg
Nicotine	Smoking cessation	1 to 15mg
Omeprazole	Proton pump inhibitor	10 to 20mg

B. Film Forming Polymers

Water soluble polymers are utilized such as HPMC E-3, E-5 E-15, K-3., Methyl cellulose A-3, A-6 and A-6, Carboxymethylcellulose, pullulan, maltodextrin, hydroxypropylcellulose cekol 30, polyvinyl alcohol etc. for the preparation of the oral soluble film. They can be utilized individually and also in combination, to impact the desired properties into the film.

The characteristic properties of the film forming polymer

- It must have good shelf life.
- It must have good wetting property.
- It shall have good spread ability property.
- It must not aid in cause secondary infections in the oral mucosa/ dental region.
- It must have a good mouth feel property.
- Polymer employed must be non-toxic, non-irritant and devoid of leach able impurities.

C. Plasticizers

It is an essential ingredient in oral film as it imparts flexibility to the film by reducing its brittleness and improves the strip property for preparing the oral film. It also improves the flow of polymer and enhances the strength of the polymer. The selection of plasticizer will rely upon its compatibility with the polymer and also solvent employed in

the casting of the strip. Plasticizers are frequently used in the concentration of 0-20%w/w of dry polymer weight.

D. Strip Forming Polymers

The polymers in the formulation can be used alone are in combination to obtain the desired strip properties. The film obtained should be tough enough so that they won't be any damage while handling or during transportation. The robustness of the strip will rely upon the type of polymer and its amount. A variety of polymers are available for the preparation of oral strip. On the other side, fast dissolving strip dosage form must have the ability to disintegrate in seconds when placed in mouth and deliver the drug to the oral cavity instantaneously. Various polymers used in the formulation of oral strips are given in table 2 .Of the various polymers available pullulan, gelatin and hydromellose are most commonly used for preparation of oral strip. Atleast 45% w/w of polymers should generally be present based on the total weight of dry oral strip.

Table 2: Strip Forming Polymers

Strip Forming Polymers	Hydroxyl propyl methyl cellulose (hypromellose)	Hydroxyl propyl cellulose	Starch and modified starch	Pullulan	Gelatin	Carboxymethyl cellulose
Synonym	HPMC, methocel, metolose, benecel.	Hydroxy prpoply ether, hyprolose, klucel, Nisso HPC	Amido, amylum, pharmGel, fluftex W, Instant pure-Cote,Melogel	Pullulan,1,6α linked maltotriose	Byco, cryogel, instgel, solugel	Akulell, blanose, aquasorb, CMCsodium
Molecular weight	10000-1,500,000	50000-1,250,000	50,000-1,60,000	8000-2,000,000	15,000-2,50,000	90,000-7,00,000
Solubility	Soluble in cold water, forming a viscous colloidal solution, in soluble in chloroform, ethane	It is freely soluble in water below 38^{0}C forming a smooth, clear, colloidal solution	Starch is insoluble in cold water and ethanol. It swells in water by about 5 to 10% at 37^{0}C	It is soluble in hot as well as cold water	Soluble in glycerin, acid and alkali. Swells in water and softens. It is soluble in hot water.	It is easily dispersed in water to form a clear or colloidal solution
Film forming ability	It has a film forming ability in 2 to 20% w/w concentration	5%w/w solution is generally used for film coating	Modified starches have a property to form quick dissolving films	5 to 25%w/w solution forms flexilble films	It has very good film forming property.	Carboxymethylcellulose as good film formomg property
Viscosity	Viscosity of various grades ranges from 3mPas-1,00,000mPas	75mPas-6500mPas depending upon the polymer grade	2%w/v aqueous dispersion of starch provides 13mPas viscosity	The viscosity (10%w/w,30^{0}C) of pullulan was 100 – 180mm^2	4.3-4.7mPas for a 6.67%w/w aqueous solution at 60^{0}C	The 1%w/w aqueous solution as viscosities in the range of 5 to 13,000 mpPas.
Melting point	Browns at 190 to 200^0 C. Glass transition temperature is 170 to 180^{0}C	It softens at 130^{0}C ,chars at 260-275^{0}C	It decomposes at 250^{0}C	107^{0}C		Browns at 227^{0}C chars at 252^{0}C

E. Saliva Stimulating Agent

A saliva stimulating agent is utilized to enhance the rate of production of saliva, because the saliva helps in rapid disintegration of fast dissolving film formation. Saliva stimulating agents are utilized alone as well as in combination between 2 to 6% w/w of the weight of the film[9].

F. Sweetening Agent

This is the most essential part of the food product or in pharmaceutical dosage forms. Natural as well as artificial sweetening agents are utilized to improve the palatability of the formulation. Sweetening agents commonly used either alone or in combination between the concentrations of 3 to 6%w/w[10].

G. Flavoring Agent

Selection of flavor depends on which type of drug is to be administered in the formulation. The perception of the oral disintegrating / dissolving formulation by an individual, depends on the initial flavor quality which is noticed in the first few seconds after the product has been absorbed and the after taste of the formulation which lasts for at least about 10 min. Preferable concentration of flavor 10%w/w [11, 12, 13].

H. Surfactant

Surfactants are utilized as a solubilising or wetting dispersing agent so that the film dissolves within seconds and release the active agent immediately.

I. Coloring Agent

FDA approved coloring agents are used in the manufacturing of oral dissolving films. (Not exceeding concentration levels of 1%w/w). For example: titanium dioxide.

Table 4: Formulating agents of oral dissolving films

S.No	Plasticizers	Sweetening agents	Flavouring agents	Coloring agents	Saliva stimulating agents	Surfactant
1.	Aceyl triethyl citarate	Mannitol;sorbitol	Lemon	Natural	Citric acid	Polaxamer 407
2.	Polyethylene glycol	Xylitol;polyols	Peppermint	Titanium oxide	Lactic acid	Benzalkoonism chloride
3.	Propylene glycol	Aspartame	Cinnamon	Silicon dioxide	Malic acid	Benzthonium chloride
4.	Sorbitol	Glycyrrhizin	Vanillin	Zinc oxide	Ascorbic acid	Tweens
5.	Glycerine	Saccharin;cyclamate	Menthol		Tartaric acid	Spans
6.	Citrate ester	Malitol;isomatol malitol	Wintergreen		Sodium lauryl sulphate	
7.	Triacetin	Acesulfame potassium	Orange			
8.	Triethyl citrate	Dextrose;fructose	Clove			

V. Methods used in the manufacture of fast dissolving films

One or combination of the following methods can be used to manufacture the mouth dissolving film [17].

A. Solvent casting
B. Semisolid casting
C. Hot melt extrusion
D. Solid dispersion extrusion
E. Rolling

A. Solvent casting method

In solvent casting method, water soluble polymers are dissolved in water and the drug along with other excipients are dissolved in applicable solvent and then both the solutions are mixed, stirred and finally casted in to the petri plate and dried. The specifications are given in table 5.

Table 5: Specification condition required by using solvent casting method

Mixing condition		Agitated emulsification device		Vacuum defoaming device		Coating apparatus	
Temp	20-90 ^{0}C	Flow rate	80L/h	Flow rate	80L/h	Passage time	2-8min
Agitating time	40-120 min	Agitating time	15min			Drying temp	50-130^{0}C
Rotating speed	1000-2000 rpm	Homogenizer pressure	15min			Solution temp	40-90^{0}C

The solvent casting method is given in the flow chart 1. The merits and demerits of the method are given in table 6.

Water soluble hydrocolloids dissolved in water to form homogenous viscous solution

Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear process

↓

Both mixtures are mixed to form homogenous viscous solution

↓

Degassed under vacuum

↓

Bubble free solution is coated on non-treated casting film

↓

Coated film is sent to aeration drying oven

↓

Film is cutted in to desired shape and size

Table 6: Merits and demerits of solvent casting method

Merits	Demerits
Great uniformity of thickness. Great clarity then extrusion. More flexibility. Better physical properties. Finished film thickness is typically 12-100µm.	Polymer must be soluble in a volatile solvent or water. Optimum viscosity should be formed.

B. Semisolid Casting

In this method a solution of water soluble film forming polymer should be prepared and the resulting solution should be added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was made in ammonium or sodium hydroxide. Then suitable amount of plasticizer should be added to form a gel mass. Finally, the gel mass should be casted in to the films or ribbons using heat controlled drums. The thickness of the film formed will be in the rapid of 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer must be 1:4 in this method.

C. Hot Melt Extrusion (HNE)

In this method, the drug is mixed with carriers in solid form and then the extruder having heaters melts the mixture. Finally the melt is formed in to films by the dies. There are certain benefits of hot melt extrusion [18].

- It has a fewer operation units.
- It has better content uniformity.
- It is an anhydrous process.
- Hot melt extrusion process is based on polymer with a high glass transition temperature such as PVP [14].

The pharmaceutical challenges of API can be overcome by using HME which is given in table 7.

Table 7: Determining the pharmaceutical challenges of API by Hot melt extrusion method

Problem	Solution by HME
Poor bioavailability due to poor API solubility.	Enhance dissolution.
Poor API stability during processing caused by hydrolysis.	No hydrolysis.
Poor taste of the API.	Taste-masked dosage form.
Manufacturing of film.	Prepared various type of film such as oral film, buccal film etc.

The advantages and disadvantages of HME are given in table 8.

Table 8: Advantages and Disadvantages of Hot melt extrusion method [15, 16]

Advantages	Disadvantages
Improved bioavailability of poorly soluble compounds. During processing solvents and water are not required. Cost-effective process with reduced production time and number of unit operations. Better content uniformity was obtained among granules of different size ranges.	Thermal process (drug/polymer stability). Flow properties of the polymer are necessary to processing. Limited amount of available polymer. Require high power input. The melt technique cannot be applied to heat-sensitive materials due to the evaluated temperatures involved.

D. Solid dispersion extrusion

In this method immiscible components are ejected with drug and then solid dispersions are prepared. Finally the solid dispersions are formed in to films by means of dies.

E. Rolling Method

In rolling method a solution or suspension having drug is rolled on a carrier. The solvent is mainly water and mixture of water along with alcohol. The film is dried on the rollers, cutted in to desired shapes and sizes.

VI. Evaluation of Fast Dissolving Films

A. **Thickness:** The thickness of film can be determined by micrometer screw gauge at different strategic locations (at least 5 locations). This is important to determine uniformity in the thickness of the film as it is directly related to the accuracy of dose in the film.

B. **Dryness Test/Tack Tests:** About eight levels of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print free.

C. **Tensile Strength:** Tensile strength is the maximum stress in seconds applicable to a point at which the film specimen breaks [20]. It is measured by the applied load at rupture divided by the cross-sectional area of the film as given below:

Where

$$\text{Test strength} = \frac{\text{Load at failure} \times 100}{\text{Film thickness} \times \text{film width}}$$

D. **Percent Elongation:** When stress is applied, a film sample stretches and this is indicated to as strain. Strain is basically the deformation of film divided by original dimension of the sample. As the elongation of film increases, the plasticizer content increases [21, 22]. Where

$$\text{Percent elongation} = \frac{L \cap 100}{L_0}$$

L = Increase in length of film L_0 = Initial length of film

E. **Tear Resistance:** The maximum stress or force (that is meter generally found near the onset of tearing) needed to tear the film is noted as the tear resistance value in Newton (or pounds-force).

F. **Young's Modulus:** Young's modulus or elastic modulus is the measure of stiffness of film. It is determined as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Film thickness} \times \text{Cross} - \text{head speed}}$$

Hard and brittle film determines a high tensile strength and Young's modulus with small elongation.

G. **Folding Endurance:** Folding endurance is demonstrated by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is reported as the folding endurance value [23].

H. **Stickiness Determination:** It is determined by texture method usually used for measurement of the tack of pressure sensitive adhesives.

I. **Swelling Index [24]:** It is useful in case of film formulation having gelling property and determined by two methods.

J. **Linear Expansion Coefficient in Water:** The film (1 x 1 cm^2) was placed in a petridish and immersed in 10 ml of distilled water. Specimens were taken at 30, 40, 60, 80, 100, 120, 140, 160 and 180 seconds and the size of the side length was measured. The linear expansion coefficient (L %) was defined as

$$L\ \% = \left(\frac{L_a - L_b}{L_b}\right) \times 100$$

Where- L_a = Side length after immersion, L_b = Side length before immersion

K. **Amount Absorbed:** The film is weighed (W_a) and is placed in the stainless steel mesh basket. The weight after immersion in water is determined (W_c).Similarly weight after immersion of basket without film is determined (W_c).The amount absorbed (W) is determined by following equation:

$$W(g/g) = \frac{(W_b - W_a - W_c)}{W_1}$$

L. **Contact Angle Measurement [25]:** Time dependent Contact angle is determined by an optical contact angle meter. The contact angle determined by different methods like the two tangential methods, a height width ratio, the circle fitting and sessile drop fitting. It's prediction for wetting behavior, disintegration and dissolution of oral films.

M. **Disintegration Time:** The disintegration time limit ie: ≤ 30s for orally disintegrating tablets was described in centre for drug evaluation and research (CDER) guidance can be applied to fast dissolving oral film. Although no official guidance is described for oral fast disintegrating films/strips, this may be utilized as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be utilized for this study. Typical disintegration time for film is 5-30s.

N. **Dissolution Test:** Dissolution testing can be operated using the standard basket or paddle apparatus determined in any of the pharmacopoeia. The volume of dissolution medium should be selected as per the sink conditions along with highest dose of the API [26]. Many times the dissolution test can be challenging due to the tendency of the film to float onto the dissolution medium when the paddle apparatus is employed. So mostly we utilize the basket apparatus for evaluation.

O. **Dissolution rate via conductivity:** Within one minute, the fast dissolving oral films dissolve completely. Currently, mostly of the marketed oral films contain ionisable components. For greater resolution monitoring of the dissolution of fast dissolve oral films, they measure conductivity of the dissolution medium.

P. **Assay/Drug content and content uniformity:** This is calculated by any standard assay method described for the particular API in any of the standard pharmacopeia. Content uniformity is calculated by estimating the API content in the individual film. The content uniformity limit was in the range of 85-115%.

Q. **Organoleptic Evaluation:** This is important step in case of most oral formulations due to its more residence time in the oral cavity. The product must possess the desired features of sweetness and flavor which is acceptable to a large mass of population. For evaluation of psychophysical products, special controlled human taste panels are utilized. In-vitro methods of utilizing taste sensors, specially designed apparatus along with drug release by modified pharmacopoeial methods being utilized for this purpose [27]. Experiments utilizing electronic tongue measurements have also been reported to distinguish between the sweetness levels in taste-masking formulation.

R. **Morphology Studies [28]:** Scanning electron microscopy (SEM) study specifies the differences between upper and lower side of the films. It also helps in demonstration of the distribution of API. Near-infrared chemical imaging (NIR-CI) study helps in demonstrating the difference between drug distributions in drug loaded films and recrystallization.

VII. Technologies to Produce Films

A. ***Soluleaves™*** technology is utilized to produce a range of oral delivery films that can incorporate active ingredients, colours and flavours. Soluleaves™ films can be dissolved rapidly on contact with saliva and instantly releases the active ingredients and flavours. For pharmaceutical uses this method of administration is mainly useful for paediatric or elderly patients who may have difficulty swallowing traditional tablets or capsules. The delivery system can be utilized for the cough/cold, gastrointestinal and pain therapeutic areas as well as delivering nutritional products. Soluleaves™ films can also be designed to attach to mucous

membranes and to release the active ingredient slowly over 15 minutes.

B. ***Wafertab™*** is a drug delivery system that administers pharmaceutical actives into an ingestible filmstrip. The system gives rapid dissolution and release of actives when the strip comes into contact with saliva in the mouth. The Wafertab™ filmstrip can be flavoured for furthermore improved taste masking. The active ingredient is accurately dosed and integrated into the body of a pre-manufactured Xgel™ film, thus blocking the exposure to unnecessary heat and moisture and potentially enhancing product stability. The Wafertab™ system accommodates itself for many possibilities of innovative product design, enabling multiple films with different actives to be bonded together. Wafertab™ can be processed in a variety of shapes and sizes and it is an ideal method for delivery of medicines, which needs fast release, or for use by patients who have difficulty in swallowing.

C. ***Foamburst™*** is a distinct variant of the Soluleaves™ technology where an inert gas goes into the film during production. This concludes in a film with a honeycombed structure, which dissolves fastly giving a novel mouth sensation. Foamburst™ has intrigued interest from food and confectionary manufacturers as a means of carrying and releasing flavours.

D. ***Xgel™*** film is at the centre of Meldex International's intellectual property, utilized in all its film systems along with its ingestible dosage delivery technologies. Xgel™ film gives unique product benefits for healthcare and pharmaceutical products, it is non animal- derived, accepted on religious grounds and is applicable for vegetarians; the film is genetically modified organisms (GMO) free and continuous production processing gives an economic and competitive manufacturing platform. Xgel™ film can be taste masked, coloured, layered, and efficient of being enteric properties and also having the ability to administer active pharmaceutical ingredients. The Xgel™ film systems can be manufactured to encapsulate any oral dosage form and also can be solubilized in either cold or hot water. Xgel™ film is contained of a range of different water-soluble polymers, particularly optimised for the intended use.

VIII. Packaging of the Films:

The fast dissolving system can be packaged utilizing various options, such as single pouch, blister card with multiple units, multiple-unit dispenser and continuous roll dispenser. There are some patented packaging systems for oral film given in the table 9.

Table 9: Oral films containing patented packaging systems

Packaging	Company
RapidCard	Labtec
Core-peel^{R}	Amcor Flexibles

IX. Clinical and Regulatory Aspects:

In the US Food and Drug Administration, if the product is bioequivalent to that of the existing oral product of the drug, an Abbreviated New Drug Application (ANDA) route is followed. There are no clinical studies related in this generic approval process (section 505(j) of the Food, Drug and Cosmetics Act). The example of aforementioned case would be a comparative bioequivalence between ODT formulation and OTF product. However, developed oral film product may also display a different target pharmacokinetic profile correlated to the existing marketed product. The OTF is classified as “new dosage form” and the section 505(b)(2) approval process needs to be followed. In this case, a new clinical study would be needed. The benefit of a new clinical study is that it would award three years of marketing exclusivity to the product. In the Europe, Marketing Authorization approval (Abridged Application) is important as per the European Medicines Evaluation Agency guidelines. Either of the two modes i.e. the decentralized procedure or the mutual recognition route can be accepted. The Ministry of Health, Labor and Welfare is primarily answerable for product approvals in Japan.

Table 10: various patents in United States on fast dissolving oral films/strips

Title	United States Patent	Issued	Inventors	Assignee	Appl.No	Filed
Fast dissolving orally consumable films containing a taste masking agent	7,648,712	Jan 19,2010	Bess; William S. (Edison, NJ), Kulkarni; Neema (Randolph, NJ), Ambike; Suhas H. (West Hill, CA), Ramsay; Michael P. (Ajax, CA)	McNeil-PPC (Skillman, NJ)	11/429,547	May 5, 2006
Process for manufacturing thin film strip	6,824,829	Nov.30, 2004	Nov.30, 2004 Craig j.berry	Aupac packaging,inc.	10/226,451	Aug.23,2002
Fast dissolving orally consumable film	7,025,983	Apr.11,2006	Sau Hung Spence Leung,Robert S. Leone,Lori D. Kumar, Neema Kulkarni,	Warner Lambert Company LLC.	09/836,474	Apr.18,2001
Fast dissolving orally	2003/0208931	Nov. 13,	Albert F. Sorg Lori D. Kumar,	Warner Lambertv	10/423,398	Apr.25,2003

consumable film containing the sweetner		2003	Neema Kulkarni,. Albert F. Sorg	Company LLC.		
Fast dissolving film for oral administration of drugs	2004/020	Oct.21,2004	David R.Friend, l Aaron W. Levine, Kerrie L. Ziegler, Emmanuel Manna	William Squire,Esq	10/744,479	Dec. 23, 2003
Fast dissolving orally consumable films containing a modified starch for improved heat and moisture resistance	2004/0247648	Dec. 9,2004	David John Fadden Neema Kulkarni, Albert F. Sorg	Pfizer, Inc.	10/838,045	May 3, 2003
Oral fast dissolving film for erectile dysfunction bioactive agents	2009/0047330	Feb. 19,2009	Ramesh bangalore	–	12/228702	Oct.9,2008
Water soluble film for oral administration with instant wettability	5,948,430	Sep.7,1999	Horst George Jian Hwa Guo, Anthony Serino	LTS Lohman Therapie-systeme GmbH Zerbe, LTS Lohman	08/904,607	Aug 1,1997
Water soluble sheet composition	6,800,295	Oct 5,2004	Priscilla S. Fox	The Dial Corporation	10/267,235	Oct. 9,2002
Method for producing film type dosage	6,800,329	Oct. 5,2004	Michael Horstmann, Wolfgang Laux, Horst Dzekan,Katja Zinndorf	, LTS Lohman Therapie-systeme AG	10/314,549	Dec. 9,2002
Process for manufacturing thin film strips	6,824,829	Nov. 30,2004	Craig J. Berry, Walter klauser	Acupac packaging,Inc.	10/226,451	Aug 23,2002
Flavoured film	7,132,113	Nov.7,2006	Horst G. Zerbe, Fadia Al- Khalil	Intelgenx Corp.	10/123,142	Apr.16,2002
Thin film strips	7,241,411	Jul.10,2007	Craig J. Berry, Walter klauser	Acupac packaging,Inc	10/922,502	Aug.20,2004
Disintegrable films for diagnostic devices	7,470,397	Dec.30,2008	William G.Meathrel, Nathan A. Meyer,Scott D.Barnhart,Cathy M.Moritz,Andrew P.Full,Susan R.Newsom, Mary Robertson	Adhesives research,inc	10/970,383	Oct.22,2004
Film comprising nitroglycerine	20100215774	August 26, 2010	Maibach, Todd	–	–	February 8,2008
Pullulan film composition	7,267,718	Sep.11,2007	Robert Scott, Dominique Cade	Warner Lambert Company LLC.	10/941,182	Sep.15,2004

X. CONCLUSION

Oral thin films are predetermined for application in the oral cavity as they are innovative and promising dosage form particularly for use in the pediatrics' and geriatrics. They integrate the greater stability of a solid dosage form and the good applicability of a liquid and thus connect the gap between two sides and liquid dosage forms into an elegant stable and effective delivery vehicle. So they are of great significance during the emergency cases such as allergic reactions and asthmatic attacks whenever immediate onset of action is desired. Today, OTSs are a proven and authorized technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early-to-mid-development stages for prescription drugs.

REFFERENCES

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